

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**LISTING OF CLAIMS:**

1. *(withdrawn)*: A method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition, the method comprising determining a genotype of said subject which includes one or more polymorphic sites in the subject's protein C sequence; EPCR sequence or a combination thereof, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition.
2. *(withdrawn)*: The method of claim 1, wherein the polymorphic site is
  - (a) position 4732 of SEQ ID NO:1; or position 4054 of SEQ ID NO:2; or a polymorphic site in linkage disequilibrium thereto; or
  - (b) a combination of Protein C and EPCR sequences, wherein said polymorphic sites are at two or more of positions selected from 4732 of SEQ ID NO:1; 4054 of SEQ ID NO:2; 2418 of SEQ ID NO:1; and a polymorphic site in linkage disequilibrium thereto.
3. **CANCELED**
4. *(withdrawn)*: The method of claim 2, wherein
  - (a) the polymorphic site in linkage disequilibrium with position 4732 may be selected from positions 4813, 6379, 6762, 7779, 8058, 8915 and 12228 of SEQ ID NO: 1;
  - (b) the polymorphic site in linkage disequilibrium with position 4054 may be selected from positions 2973, 3063, 3402, 4946, 5515 and 6196 of SEQ ID NO: 2;
  - (c) the polymorphic site in linkage disequilibrium with position 2418 may be selected from positions 1386, 2583 and 3920 in SEQ ID NO: 1;
  - (d) the polymorphic site in linkage disequilibrium with position 4732 may be selected from a combination of two polymorphic sites, which sites occur at any of the following combinations of positions in SEQ ID NO:1:
    - 9198 and 5867;
    - 9198 and 4800;
    - 3220 and 5867; and
    - 3220 and 4800;and/or
  - (e) the polymorphic site in linkage disequilibrium with position 2418 may be selected from a combination of two polymorphic sites, which sites occur at any of the following combinations of positions in SEQ ID NO:1:
    - 5867 and 2405;
    - 5867 and 4919;
    - 5867 and 4956;

5867 and 6187;  
5867 and 12109;  
4800 and 2405;  
4800 and 4919;  
4800 and 4956;  
4800 and 6187; and  
4800 and 12109.

**5 to 9: CANCELED**

10. *(withdrawn)*: The method of claim 1, further comprising obtaining protein C sequence information or EPCR sequence information for the subject.

11. *(withdrawn)*: The method of claim 1, wherein the genotype is determined using a nucleic acid sample from the subject.

12. *(withdrawn)*: The method of claim 11, further comprising obtaining the nucleic acid sample from the subject.

13. *(withdrawn)*: The method of claim 1, wherein said genotype is determined using one or more of the following techniques:

- (a) restriction fragment length analysis;
- (b) sequencing;
- (c) hybridization;
- (d) oligonucleotide ligation assay;
- (e) ligation rolling circle amplification;
- (f) 5' nuclease assay;
- (g) polymerase proofreading methods;
- (h) allele specific PCR; and
- (i) reading sequence data.

14. *(withdrawn)*: The method of claim 1, wherein

- (a) the genotype of the subject is indicative of a decreased ability to recover from the inflammatory condition, or
- (b) the subject is critically ill and the genotype is indicative of a prognosis of severe cardiovascular or respiratory dysfunction.

**15. CANCELED**

16. *(withdrawn)*: The method of claim 14, wherein the genotype comprises

- (a) at least one of the following single polymorphic nucleotides or combinations of polymorphic nucleotides at the indicated positions of SEQ ID NO: 1:  
4732 C;  
4813 A;  
6379 G;

6762 A;  
7779 C;  
8058 T;  
8915 T;  
12228 T;  
9198 C and 5867 A;  
9198 C and 4800 G;  
3220 A and 5867 A; and  
3220 A and 4800 G, or  
1386 T;  
2418 A;  
2583 A;  
3920 T;  
5867 A and 2405 T;  
5867 A and 4919 A;  
5867 A and 4956 T;  
5867 A and 6187 C;  
5867 A and 12109 T;  
4800 G and 2405 T;  
4800 G and 4919 A;  
4800 G and 4956 T;  
4800 G and 6187 C; and  
4800 G and 12109 T; and

- (b) at least one of the following EPCR polymorphic nucleotides at the indicated positions of SEQ ID NO: 2:

6196 G;  
5515 T;  
4946 T;  
4054 T;  
3402 G;  
3063 G; and  
2973 C.

**17. CANCELED**

18. *(withdrawn)*: The method of claim 16, wherein the genotype of the subject is indicative of an increased ability to recover from the inflammatory condition.

19. *(withdrawn)*: The method of claim 18, wherein the subject is critically ill and the genotype is indicative of a prognosis of mild cardiovascular or respiratory dysfunction.

20. *(withdrawn)*: The method of claim 14, wherein the genotype comprises

- (a) at least one of the following genotypes or genotype combinations within SEQ ID NO:1:

4732 T;  
4813 G;  
6379 A;  
6762 G;  
7779 -;  
8058 C;  
8915 G;  
12228 C;  
9198 A and 5867 G;  
9198 A and 4800 C;  
3220 G and 5867 G; and  
3220 G and 4800 C,

or

1386 C;  
2418 G;  
2583 T;  
3920 C;  
5867 G and 2405 C;  
5867 G and 4919 G;  
5867 G and 4956 C;  
5867 G and 6187 T;  
5867 G and 12109 C;  
4800 C and 2405 C;  
4800 C and 4919 G;  
4800 C and 4956 C;  
4800 C and 6187 T; and  
4800 C and 12109 C;

and

- (b) at least one of the following genotypes within SEQ ID NO: 2:
- 6196 C;  
5515 C;  
4946 C;  
4054 C;  
3402 C;  
3063 A; and  
2973 T.

## 21 CANCELED

22. *(withdrawn)*: The method of claim 1, wherein the inflammatory condition is selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration

pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for subjects undergoing major surgery or dialysis, subjects who are immunocompromised, subjects on immunosuppressive agents, subjects with HIV/AIDS, subjects with suspected endocarditis, subjects with fever, subjects with fever of unknown origin, subjects with cystic fibrosis, subjects with diabetes mellitus, subjects with chronic renal failure, subjects with bronchiectasis, subjects with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, subjects with febrile neutropenia, subjects with meningitis, subjects with septic arthritis, subjects with urinary tract infection, subjects with necrotizing fasciitis, subjects with other suspected Group A streptococcus infection, subjects who have had a splenectomy, subjects with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELLP syndrome, mycobacterial tuberculosis, Pneumocystis carinii, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and cirrhosis.

23. *(withdrawn)*: The method of claim 22, wherein the inflammatory condition is SIRS.

**24 to 31 CANCELED**

32. *(withdrawn)*: A method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition, the method comprising determining a genotype at one or more polymorphic sites in the protein C sequence or EPCR sequence for each subject, wherein said genotype is indicative of the subject's ability to recover from the inflammatory condition and sorting subjects based on their genotype.

33. *(withdrawn)*: The method of claim 32 further comprising, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the inflammatory condition.

34. *(withdrawn)*: The method of claim 33, further comprising comparing subject response to the candidate drug based on genotype of the subject.

**35. CANCELED**

36. *(currently amended)*: A method of treating an inflammatory condition in a human subject in need thereof, the method comprising:

- (a) selecting a human subject having a risk genotype for said inflammatory condition in his ~~their~~ protein C sequence or EPCR sequence, wherein the risk genotype is located at a polymorphic site at one or more of the following positions:
  - (i) 4732 of SEQ ID NO:1;
  - (ii) 4054 of SEQ ID NO:2,
  - (iii) 2418 of SEQ ID NO:1, or
  - (iv) a single polymorphic site in linkage disequilibrium (LD) with position 4732; 4054; and 2418, which single polymorphic site is found, respectively, at
    - (1) for sites in LD with position 4732 of SEQ ID NO:1: position 4813, 6379, 6762, 7779, 8058, 8915 or 12228 of SEQ ID NO:1;
    - (2) for sites in LD with position 4054 of SEQ ID NO:2: position 2973, 3063, 3402, 4946, 5515 or 6196 of SEQ ID NO:2; or
    - (3) for sites in LD with **position 2418 of SEQ ID NO:1:** position 1386, 2583 or 3920 in SEQ ID NO:1; or
  - (v) a combination of two sites in SEQ ID NO:1 which are in LD with position 4732 in SEQ ID NO:1 selected from the group of positions consisting of:
    - (1) 9198 and 5867;
    - (2) 9198 and 4800;
    - (3) 3220 and 5867; and
    - (4) 3220 and 4800;
  - (vi) a combination of two sites in SEQ ID NO:1 which are in LD with position 2418 in SEQ ID NO:1, selected from the group of positions consisting of:
    - (1) 5867 and 2405;
    - (2) 5867 and 4919;
    - (3) 5867 and 4956;
    - (4) 5867 and 6187;
    - (5) 5867 and 12109;
    - (6) 4800 and 2405;
    - (7) 4800 and 4919;
    - (8) 4800 and 4956;

(9) 4800 and 6187; and

(10) 4800 and 12109, and

- (b) administering to said subject selected in (a) activated protein C ~~an anti-inflammatory agent or an anti-coagulant agent,~~

wherein the inflammatory condition is sepsis, septic shock or systemic inflammatory response syndrome (SIRS).

**37 to 43: CANCELED**

44. *(previously presented)*: The method of claim 36, further comprising determining the subject's APACHE II score as an assessment of subject risk.

45. *(previously presented)*: The method of claim 36, further comprising determining the number of organ system failures for the subject as an assessment of subject risk.

46. *(previously presented)*: The method of claim 44, wherein, an APACHE II score  $\geq 25$  is indicative of increased risk.

47. *(previously presented)*: The method of claim 45, wherein two or more organ system failures are indicative of increased subject risk.

**48. CANCELED**

49. *(currently amended)*: The method of ~~claim 36~~ claim 48, wherein the inflammatory condition is SIRS ~~systemic inflammatory response syndrome~~.

**50 to 57: CANCELED**

58. *(currently amended)*: The method of claim 36, wherein the risk genotype is selected from the group consisting of the following genotypes:

- (a) ~~the following genotypes~~ in SEQ ID NO:1:

4732 C;

4813 A;

6379 G;

6762 A;

7779 C;

8058 T;

8915 T;

12228 T;

9198 C and 5867 A;  
9198 C and 4800 G;  
3220 A and 5867 A;  
3220 A and 4800 G  
1386 T;  
2418 A;  
2583 A;  
3920 T;  
5867 A and 2405 T;  
5867 A and 4919 A;  
5867 A and 4956 T;  
5867 A and 6187 C;  
5867 A and 12109 T;  
4800 G and 2405 T;  
4800 G and 4919 A;  
4800 G and 4956 T;  
4800 G and 6187 C; and  
4800 G and 12109 T;  
or and

(b) ~~the following genotypes~~ in SEQ ID NO:2:

6196 G;  
5515 T;  
4946 T;  
4054 T;  
3402 G;  
3063 G; and  
2973 C.

**59. CANCELED**

60. *(currently amended)*: The method of claim 58, wherein the genotype of the subject is indicative of an increased risk of poor outcome from ~~an~~ the inflammatory condition.

61. *(currently amended)*: The method of claim 60, wherein the subject who has ~~having an~~ increased risk of poor outcome from ~~an~~ the inflammatory condition is preferentially selected for administration of the activated protein C ~~anti-inflammatory agent or the anti-coagulant agent~~.

62. *(currently amended)*: The method of claim 36, wherein the genotype for a decreased risk is selected from the group consisting of the following genotypes;



(a) ~~the following genotypes~~ in SEQ ID NO: 1:

4732 T;  
4813 G;  
6379 A;  
6762 G;  
7779 -;  
8058 C;  
8915 G;  
12228 C;  
9198 A and 5867 G;  
9198 A and 4800 C;  
3220 G and 5867 G;  
3220 G and 4800 C;  
1386 C;  
2418 G;  
2583 T;  
3920 C;  
5867 G and 2405 C;  
5867 G and 4919 G;  
5867 G and 4956 C;  
5867 G and 6187 T;  
5867 G and 12109 C;  
4800 C and 2405 C;  
4800 C and 4919 G;  
4800 C and 4956 C;  
4800 C and 6187 T; and  
4800 C and 12109 C; ~~or and~~

(b) ~~the following genotypes~~ in SEQ ID NO: 2:

6196 C;  
5515 C;  
4946 C;  
4054 C;  
3402 C;  
3063 A; and  
2973 T.

63. CANCELED

64. *(currently amended)*: The method of claim 62, wherein the genotype of the subject is indicative of a decreased risk of poor outcome from ~~an~~the inflammatory condition.

65. *(currently amended)* The method of claim ~~of~~ 64, wherein the subject who has~~having~~ a decreased risk of poor outcome from ~~an~~the inflammatory condition is preferentially not selected for administration the activated protein C ~~anti-inflammatory agent or the anti-coagulant agent~~.

**66. to 67. CANCELED**

68. *(currently amended)*: The method of claim 36, wherein the activated protein C ~~anti-inflammatory or anti-coagulant agent~~ is drotrecogin alfa activated.

**69 to 87: CANCELED**

88. *(new)*: The method of claim 36, wherein the risk genotype is located at a polymorphic site at one or both positions 4732 of SEQ ID NO:1 and 4054 of SEQ ID NO:2.

89 *(new)* A method of administering activated protein C to a selected human subject, comprising, administering activated protein C to a subject with a risk genotype who is selected for said administration on the basis of a protein C or EPCR genotype which is characterized by a polymorphic site at one or more of the following positions:

- (a) position 4732 of SEQ ID NO:1;
- (b) position 4054 of SEQ ID NO:2;
- (c) position 2418 of SEQ ID NO:1;
- (d) a single polymorphic site in LD with one of said three positions, or which single polymorphic sites are:
  - (i) for sites in LD with position 4732 of SEQ ID NO:1, positions 4813, 6379, 6762, 7779, 8058, 8915 or 12228 of SEQ ID NO: 1;
  - (ii) for sites in LD with position 4054 of SEQ ID NO:2, position 2973, 3063, 3402, 4946, 5515 or 6196 of SEQ ID NO: 2; or
  - (iii) for sites in LD with position 2418 of SEQ ID NO:1, position 1386, 2583 or 3920 in SEQ ID NO: 1; or
- (e) a combination of two sites in SEQ ID NO:1 which are in LD with position 4732 in SEQ ID NO:1, selected from the group of positions consisting of:
  - (1) 9198 and 5867;
  - (2) 9198 and 4800;

- (3) 3220 and 5867; and
- (4) 3220 and 4800, and/or
- (f) a combination of two sites in SEQ ID NO:1 which are in LD with position 2418 in SEQ ID NO:1, is selected from the group of positions consisting of:
  - (1) 5867 and 2405;
  - (2) 5867 and 4919;
  - (3) 5867 and 4956;
  - (4) 5867 and 6187;
  - (5) 5867 and 12109;
  - (6) 4800 and 2405;
  - (7) 4800 and 4919;
  - (8) 4800 and 4956;
  - (9) 4800 and 6187; and
  - (10) 4800 and 12109.